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THE TOXINS OF INTESTINAL OBSTRUCTION *

FRASER B. GURD

(From the Laboratory of Experimental Medicine, McGill University, Montreal.)

During the past two years a very considerable number of valuable observations have been made on the nature of the factors which underlie the fatal termination so frequently encountered in cases of obstruction of the intestinal tract. Previous to 1911, although the fact that occlusion of the gut lumen is followed, within a comparatively short time, by a characteristic chain of symptoms—especially those commonly associated with shock—was generally recognized, relatively little experimental work had been done which would throw light on the causes of death in this affection. Within the last two years, however, several groups of investigators have approached the question experimentally from different points of view, and so at the present time this subject appears to be rapidly approaching a solution.

It is the author's intention to record a certain number of experiments which he believes to have a direct bearing on this subject, rather than to enter into a detailed consideration of the various data obtained by different writers on the subject.

Of the views relative to the mode of death in cases of simple acute intestinal obstruction that which assumes a bacteriemia has been pretty generally disproven and is now abandoned. The remaining opinions are those of Hartwell and Hoguet[1] "that the enormous loss of water due to the vomiting is the essential factor," and that of Whipple, Stone and Burnheim who claim that death in cases of intestinal obstruction is due to the absorption from the lumen of the gut of a toxic substance, as yet not positively identified, which is potent to lead to the death of normal animals if injected intravenously or intraperitoneally.

Briefly, Hartwell and Hoguet in their experiments took pains to so occlude the gut that the vascularization of the latter was not interfered with and under these circumstances the death of the animal was evidently due, chiefly at least, to starvation and, more particularly, to withdrawal of fluids from the tissues. Death, moreover, takes

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[1] *Am. Jour. Med. Sc.*, 1912, 143, p. 357; *Jour. Am. Med. Assn.*, 1912, 59, p. 82.

place under such circumstances at the end of from three to ten days, while animals which receive large quantities of salt solution subcutaneously live for three weeks or more. As Vincent[2] has pointed out, such experiments resemble more the chronic forms of intestinal obstruction seen clinically, such as the form due to extra- and intra-intestinal tumors.

In the work of Whipple and his associates[3] isolated loops of intestine were employed. With closed, washed duodenal loops, dogs die in from twenty-four to forty-eight hours with symptoms of most profound intoxication, as evidenced by a lowering of temperature and marked drop in blood pressure, and at autopsy they present evidence of extreme splanchnic congestion. During life such dogs suffer from a bloody diarrhea more particularly if a gastro-enterostomy is performed, in which case there is also marked vomiting.

If the isolated duodenal loop is drained the evidence of intoxication is much mitigated and the dogs live for weeks or even months.

The contents of the isolated loops are usually of the consistency of pea-soup, pinkish or anchovy-sauce like in color, and are of a characteristic heavy penetrating odor. After this material is removed, heated to 60° C. to destroy bacterial life, filtered, and the filtrate introduced into a normal animal, it causes death in from three to twelve hours, or immediately, if a sufficiently large dose is employed. The animal manifests symptoms closely allied to those which occur when the closed-loop experiment is performed. There is a similar evidence of shock and diarrhea, the latter sometimes bloody. Postmortem there is the same evidence of splanchnic paralysis.

Murphy and Vincent[4] are of the opinion that the difference in the symptoms following occlusion without vascular disturbance, and those experiments in which the vessels, more particularly the veins, are interfered with, is due to alteration in the nutrition of the mucosa permitting absorption of intestinal contents to take place.

Two points, therefore, appear to have been established: (1) that under certain circumstances of occlusion of the gastro-intestinal tract, reflex or toxic vomiting may be so marked as to lead to the death of the affected animal as the result of the consequent withdrawal of water from the tissues, and (2) that there is also produced in closed loops of intestine a toxic substance which rapidly leads to the death of the animal, and which acts chiefly through inducing extreme splanchnic congestion.

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[2] *Jour. Am. Med. Assn.*, 1912, 59, p. 86.

[3] *Johns Hopkins Hosp. Bull.*, 1912, 23, p. 159; *Jour. Exper. Med.*, 1913, 17, pp. 286, 307.

[4] *Jour. Am. Med. Assn.*, 1912, 59, p. 86.

The author's experiments, a certain number of which are given later, prove that it is possible to induce the production in the mucosa and within the intestinal lumen, of a similar poisonous body although there is no mechanical obstruction to the gut lumen.

These experiments are the outcome of an observation of the similarity in gross appearance of the intestinal contents, and of the manner of death in dogs which had been operated on by Dr. E. M. von Eberts and Dr. W. H. P. Hill in an attempt to partially occlude the lumen of the portal vein by means of a fascial band. Although these experiments were undertaken with an altogether different end in view, it was noted that in those animals in which the band was applied so tightly as more or less completely to obliterate the vein, death occurred within fifteen to thirty-six hours, and that at autopsy the intestines contained a fluid similar to that found in cases of acute intestinal obstruction. This material was tested after the manner of Whipple's experiments and was found to possess similar toxic properties. Since, in these cases, the development of the poisonous material depended exclusively on vascular disturbance of the gut wall a number of animals were operated on and the portal veins or its branches ligated. In all of these operated animals the same type of fluid, which possessed the same toxic properties as the fluids found in closed duodenal loops, was discovered.

Dogs in which the portal vein, or the branches thereof draining the upper half of the intestinal tract, was ligated, died regularly within fifteen to eighteen hours. The animals never completely recovered from the stupor of anesthesia and were frequently found dead in exactly the same position in the cage as when returned from the operating room. The intestines, pancreas, and kidneys were found deeply cyanosed and the heart blood unduly fluid. The lumen of the intestine contained fluid blood-stained material, as a rule of a more watery consistency and deeper purple color than that found in cases of gut occlusion. The intestinal contents were collected from such animals and the cyanosed mucosa scraped off and placed in saline solution under toluol for extraction. The result obtained by employing this extract for intravenous inoculation into normal dogs is given in the following protocols.

Experiment 5 T.—Collie bitch, weight 40 lbs. Injection made into left femoral vein of 25 c.c. filtered fluid prepared from intestinal scrapings and blood-stained contents from Dog 4 T. Scrapings and contents of mucosa were preserved for 5 days before use in the ice chest under toluol.

During incision of thigh and isolation of vein, the dog was under light ether anesthesia but was permitted to "come out" of the anesthetic before the injection was made. Within 15 seconds before the completion of the injection, the dog became restless but almost immediately manifested evidence of most profound shock. The pulse at first became accelerated so that the beats could not be counted, but within 2 minutes the pulse became slower, and there was a marked drop in blood-pressure, as evidenced by the absence of pulse beats in the femoral artery. Death occurred in 2 minutes from the time of injection.

Immediate autopsy showed extreme venous congestion of liver, pancreas, intestinal tract, more particularly the lower part of the stomach, the duodenum and upper portion of the ileum, and the kidneys.

Experiment 12 T.—Terrier dog, 23.5 lbs. Injection of toxic material extracted from intestinal mucosa of Autopsy 152, Experiment 9 T. Material prepared by extraction of washed intestinal mucosa, in an equal weight of physiologic saline for 6 days in an ice chest under toluol with subsequent filtration. Moderate to slight autolysis of the mucosa had occurred during this time. Sphygmographic tracings were made during the early part of this experiment.

The dog received 20 c.c. of the solution in the left femoral vein, and within 90 seconds a marked drop in blood-pressure (40 mm.) occurred, accompanied by a slight increase in the pulse rate and diminution in the excursion of the pulse wave. Within 8 minutes the blood pressure had returned to normal and the dog appeared normal. He was then given a second injection of 22 c.c. which was followed by a repetition of the previous symptoms, culminating in death 1 minute after completion of the injection.

Autopsy was performed at once and revealed the characteristic evidence of splanchnic congestion.

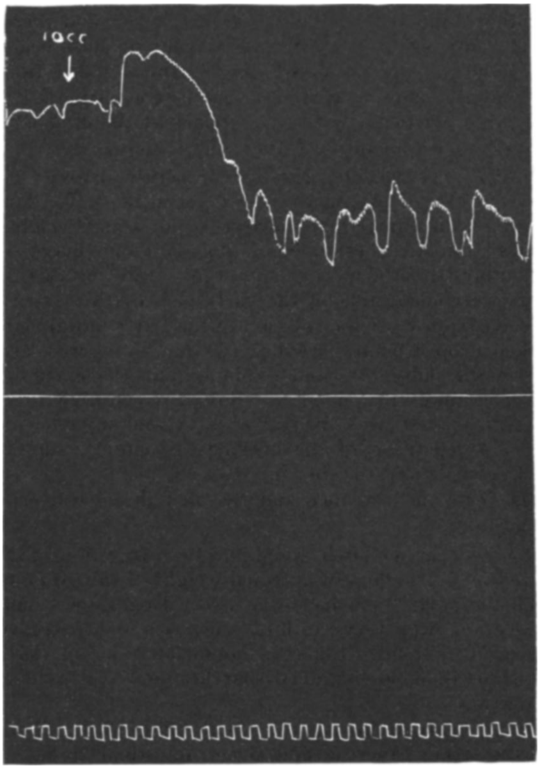
Experiment 8 T.—Terrier bitch, weight 18 lbs. Injection of 20 c.c. of filtered material prepared by extracting, in an equal weight of salt solution, mucosa from a dog, in which the portal vein had been tied. Dog showed characteristic evidence of intoxication, was very restless, and cried out. Recovery was apparently complete in 10 minutes. Eighteen hours later the animal appeared fairly well but soon showed a blood-stained diarrhea and collapsed on the floor 22 hours after injection.

Autopsy showed heart in diastole filled with fluid blood. There was moderate congestion of the liver, pancreas and upper intestinal tract. The gut lumen contained a considerable quantity of blood-stained fluid.

Experiment 15 T.—Terrier bitch, weight 16 lbs. Injection of toxic material recovered from Experiment 14 T. This material was prepared as follows: 75 c.c. of the typical material from the gut lumen was added to 25 gm. of mucosa, plus 100 c.c. of physiologic saline. This was placed in the ice chest under toluol for 48 hours, centrifuged and filtered. The experiment was carried out while the animal was attached to the blood-pressure recording apparatus. In all, the animal received 45 c.c of the diluted material in four doses—15 c.c., 15 c.c., 10 c.c., and 5 c.c. The characteristic effect of the injection is well shown in the accompanying tracing. It will be noticed that there is constantly produced a moderate initial rise in blood-pressure which precedes the marked drop noted clinically.

It is further noted that there appears to be but little cumulative effect of the toxin, at least in so far as the primary effect is concerned, nor is there any tolerance induced by repeated doses at short intervals. As the animal was not killed by doses of this size it was chloroformed.

Autopsy revealed the most extreme grade of cyanosis and congestion of the splanchnic area, simulating the appearance, in so far as the intestines and pancreas are concerned, when the portal vein is ligated. The intensity of the congestion is shown by the fact that the liver, which was removed after clamping the vessels, decreased in weight from 520 to 493 gm., when the blood was allowed to flow out, by application of gentle pressure after removing the clamps. There had thus been a gain in weight, due chiefly if not exclusively, to increased blood content, of 26 per cent.



Copy of sphygmographic tracing, Experiment 15T, showing fall in blood-pressure following initial rise after the injection of 10 c.c. of extract.

Whipple states that he has been unable to isolate a similar toxic product from normal intestinal mucosa. The author's experiments in this direction are very limited, but Experiment 16 T indicates that it is possible for a similar toxic body to be recovered from autolysis of normal mucosa.

Experiment 16 T.—Terrier dog, weight 10 lbs. 4 oz. Injection intravenously of 25 c.c. of an extract of normal dog's intestinal mucosa membrane. This extract was prepared by adding washed mucosa to an equal weight of salt solution and storing under toluol in the ice chest for 3 days. There was no odor of putrefaction nor did gross evidence of disintegration of the tissues occur in this length of time. The dog received 25 c.c. of the extract intravenously. Within 2 minutes the animal cried out and the pulse became rapid and weak. Then ensued gradual recovery after 2 or 3 minutes and at the end of 10 minutes the dog appeared normal. The following morning he appeared to be well up to 10 a. m., but was found dead at noon.

Autopsy revealed moderate venous congestion of the intestines, more particularly the stomach and duodenum. The lumen of the gut contained bloody, pasty, and fluid material.

There remain many features with regard to the nature and mode of production of the toxic substance which require further study and elucidation, including investigation such as that carried out by Whipple and his associates into the development of immunity against the toxin. The foregoing experiments are recorded simply because they appear to indicate certain factors which determine the production of the substance and in this way suggest the nature of the toxic material and its source.

CONCLUSIONS

Thus it has been proven that vascular disturbances, namely, venous stasis, are equally as potent as occlusion of the lumen in the development of a poisonous substance in the intestinal mucosa, and that the substance produced in this manner is likewise a splanchnic paralyzer.

Since the mucosa itself appears to contain a greater content of the toxic principle than does the content of the lumen, it would appear that the substance responsible for the intoxicating symptoms is the result of tissue autolysis rather than a bacterial product.

It remains to be proven whether the death of the individual in cases of portal obstruction is due to the absence of the liver activity or to the development and absorption of the intestinal toxin, or of a combination of these two factors, and the foregoing experiments indicate that the effect on the nutrition of the intestine may be a sufficient cause for the untoward manifestations.